

REMARKS

Formal Matters

Claims 1, 3-5, 13, 15 and 19-21 are pending after entry of the amendments set forth herein.

Claims 1, 3-5, 13, and 15 were examined. Claims 1, 3-5, 13 and 15 were rejected. No claims were allowed.

Claims 1, 5 and 15 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendment to the claims may be found throughout the specification, in particular at the following locations page 5, lines 28-30, where support for pronuclei formation and migration may be found, page 12, lines 30-31, where support for an "effective" amount of an NO-modulator may be found, page 15 line 28, where support for injections may be found, and in claim 14, as originally filed. Accordingly, no new matter is added by these amendments.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Interview summary

The Applicants wish to express their gratitude to Examiners Afremova and Saucier with Applicants representative, James S. Keddie, on June 4, 2003.

Arguments to overcome the current rejections were discussed. During the interview, Examiner Afremova indicated that the proposed amendments would allow the withdrawal of the rejections based on indefiniteness, and, subject to a further search, the withdrawal of the art-based rejections. Support for "an effective amount" of an NO-modulator was requested in the response to this Office Action, and a request was made to avoid using abbreviations in the claims.

New Matter

Claim 1, 3, 4, and 15 are objected to as assertedly containing new matter.

Without wishing to acquiesce to the correctness of the rejection, the asserted new matter has been cancelled from the claim and replaced with the phrase "maintaining said oocyte until pronuclei have formed and migrated within the cell". Since support for this subject matter is found on page 5, lines 28-30 of the specification as filed, this rejection may be withdrawn.

Rejections under 35 U.S.C. 112, second paragraph – indefiniteness

Claims 1, 3-5, 13 and 15 are rejected under 35 U.S.C. 112, as assertedly being indefinite.

Specifically, the Office Action asserts that claims 1, 5 and 15 are indefinite with respect to the concept of oocyte activation.

The claims are amended to recite pronuclei formation and migration. Pronuclei formation and migration are known markers for oocyte activation and are art understood terms that are recited in the specification. As such, the Applicants respectfully submit that the claims in question are not indefinite. The Examiner is respectfully reminded that during the aforementioned interview the Examiner indicated that this amendment would allow the withdrawal of this rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 3-5, 15 and 16 have been rejected under 35 U.S.C. §102(b) as being anticipated by Grumetto, Jawerbaum, US 6,255,109, or Herrero. The Applicants respectfully traverse this rejection.

Jawerbaum, US 6,255,109, and Herrero

Each of the rejected claims are directed to methods that involve *injecting* an NO modulator into a non-activated oocyte.

Jawerbaum, US 6,255,109, and Herrero disclose methods that involve placing oocytes into a source of exogenous NO-modulator (a so called "bath") and do not teach a method that involves *injecting* an NO modulator into a non-activated oocyte.

Since Jawerbaum, US 6,255,109, and Herrero do not *inject* an NO modulator into a non-activated oocyte, they cannot anticipate the claims.

Based on the foregoing discussion, withdrawal of this rejection with respect to Jawerbaum, US 6,255,109, and Herrero is respectfully requested.

Grumetto

Claims 1 and 15 are rejected as anticipated by Grumetto, assertedly because Grumetto discloses a method for activating oocytes that anticipates the claims.

Grumetto discloses a method in which an ascidian oocyte is microinjected with 5.7 mM SNP (an NO-donor), and the oocyte fails to activate. This is supported by Grumetto's statements on page 724 in the first paragraph of the results section that states that "5.7 mM SNP generated an inward current of...", and "The inward currents induced by SNP addition were however **never followed by the contraction of the cortex and production of the first polar body in ascidian oocytes**". (emphasis added). Since cortical contraction and production of the first polar body are markers for oocyte activation in ascidia, Grumetto did not activate an oocyte using this method.

Since the instant claims recite the step of maintaining an oocyte until pronuclei have formed and migrated within the oocyte (i.e. until the oocyte has activated), Grumetto fails to disclose an element of the claimed invention. Accordingly, since Grumetto fails to disclose an element of the claimed invention Grumetto cannot anticipate the claims.

Furthermore, while Grumetto may have microinjected an oocyte with an NO-modulator, the Applicants respectfully submit that Grumetto did not microinject a NO-modulator into an oocyte in an amount effective to activate the oocyte.

Support for an effective amount of an NO-modulator may be found throughout the instant specification, in particular in the paragraph starting on line 9 on page 17. This paragraph states: "*NO/NOS calculations* The amount of NOS or SNAP injected to effect activation is similar to that contained or produced by a single spermatozoon." In other words, an effective amount of a NO-modulator injected is similar to that contained or produced by a single sperm. This paragraph references table 1 on page 11 of the specification, in which NO levels (actually nitrite levels - a degradation product of NO) are calculated for gametes of sea urchins, and, in a great amount of detail, deduces that **the amount of SNAP injected into an oocyte to effect oocyte activation is approximately 5 μ M**, and the amount of nNOS injected into an oocyte to effect oocyte activation is approximately 0.0075 pg, which agree with the expected amounts of nitric

oxide at a site of sperm-egg fusion (7.2 μ M), and the expected amount of NOS in a sperm (0.005 pg), respectively. See page 17 lines 16 - 18. As such, the Applicants have demonstrated that an effective amount of an NO-modulator increases NO levels in an oocyte by an amount that is similar to the amount of NO produced upon sperm-egg fusion. The Applicants have provided guidance in the specification as to how these amounts can be ascertained (see page 11, lines 8, page 14 lines 23 -page 15 line 2 and the results of Table 1), and, as such, one of skill in the art ~~should be able to ascertain how much of an NO-modulator is effective to activate an oocyte.~~ Such calculated amounts may be readily tested using the methods described in the subject patent application, and known in the art.

The specification further states, on page 12 line 30, that "SNAP and nNOS are only effective over a narrow concentration range: levels above the activating concentration are ineffective, and exposure to high NO concentrations are in fact refractory to activation by sperm" and also states that calcium release does not have to be accompanied by oocyte activation (page 13 line 22). In other words, the Inventors recognized that too little or too much of an NO-modulator, when injected into an oocyte, may *not* cause the oocyte to activate, and that oocyte activation requires more than a change in Ca^{2+} levels.

Grumetto, in contrast, injected 5.7 mM sodium nitroprusside (SNP) into oocytes and the oocytes failed to undergo activation. The Applicants respectfully submit that 5.7 mM SNP used by Grumetto is a vast amount of NO-donor in comparison to the 5 μ M SNAP used in the subject methods (over a thousand times more, in molar units), and, as such, Grumetto did not inject an NO-modulator in an amount effective for oocyte activation. Since Grumetto did not inject an NO-modulator in an amount effective for oocyte activation, Grumetto cannot anticipate the claims.

In view of the foregoing discussion, the Applicants respectfully request withdrawal of this rejection of claims 1, 3-5, and 15 under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. § 103(a)

Claims 1, 3-5, 13, 15 remain rejected under 35 U.S.C. § 103(a) in view of US 6,225,109 and Herrero.

As discussed above, the rejected claims are directed to methods involving *injecting* an NO-modulator into an oocyte to effect oocyte activation.

US 6,225,109 and Herrero disclose methods that involve placing oocytes into a source of exogenous NO-modulator and do not disclose, teach or otherwise suggest a method that involves *injecting* an NO modulator into a non-activated oocyte.

Since US 6,255,109, and Herrero, together or in combination, do not disclose, teach or otherwise suggest a method that involves *injecting* an NO-modulator into a non-activated oocyte, they cannot render the instant claims obvious.

Based on the foregoing discussion, withdrawal of this rejection is respectfully requested.

Claims 1, 3-5, 13 and 15 remain rejected under 35 U.S.C. § 103(a) over Grumetto in view of Jawerbaum and US 6,077,710.

As discussed above, Grumetto is defective in that fails to teach a method by which an oocyte is injected with a NO-modulator in an amount effective to activate the oocyte.

This defect of Grumetto is not met by the disclosures of Jawerbaum and US Patent 6,077,710, which merely discuss placing an oocyte in a bath of NO-donor to obtain a change in calcium levels in the oocyte.

As such, these references, either alone or in combination, fail to teach an element of the claimed invention: a NO-modulator in an amount effective for oocyte activation.

Furthermore, as discussed in responses to previous Office Actions, one of skill in the art would have no motivation to combine the references since Grumetto teaches, at the bottom of the first column of page 724, that Grumetto's method *cannot* be used to activate oocytes.

The Applicants respectfully submit that the foregoing discussion adequately addresses this rejection of claims 1, 3-5, 13 and 15 under 35 U.S.C. § 103(a). Withdrawal of the rejection is respectfully requested.

CONCLUSION

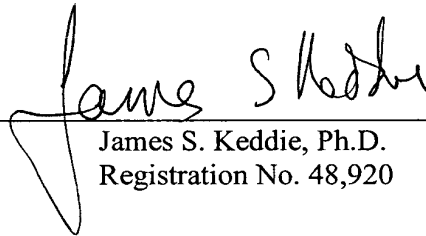
Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN209.

Respectfully submitted,
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By: _____


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